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ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,303	ROTHENBERG ET AL.	
	Examiner	Art Unit	
	ELLY-GERALD STOICA	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *19-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/30/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of claims 1-18 in the reply filed on 03/06/2008 is acknowledged. The traversal is on the ground that auto antibodies to FRs are advancement over the art. This is not found persuasive because serum antibodies against folate binding proteins (and the method of detection for them) were known in the art (Hoier-Madsen et al. –Int. J. Tiss Reac. XI (6), 327-332, 1989) and the antibodies had the same binding properties against soluble folate binding proteins and folate receptor antibodies since the latter can give raise to the former by cleavage and the epitopes are identical (Antony, AC- Blood, 79, 2807-2820, 1992). Moreover, according to the PCT rules, Applicant is allowed claims to one method of using/making for examination and if and when the claims allowable other claims are entitled to a rejoinder.

The requirement is still deemed proper and is therefore made FINAL.

Status of the claims

2. Claims 1-24 are pending. Claims 19-24 are withdrawn as being drawn to non-elected inventions. Claims 1-18 are being examined.

3. Claims 3-5, 13-15 and 18 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n).

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the independent claim 1 is indefinite because as written, in the step a., it is unclear if the acidifying of the biological sample is performed by dissociating anti-FRs antibodies, or by other means. Thus, the metes and bounds of the claim could not be determined.

6. For claim 2: it is unclear what constitutes the control. Also unclear is how does the biological sample of the preamble relate to steps a-e.

7. For claims 10-12 the metes and bounds of the “homologous species” of claims 10-12 could not be determined.

8. In claims 11 and 12: the metes and bounds of “reagents for treating said biological sample” cannot be determined.

9. Claim 13 is indefinite because it is unclear how a person of ordinary skill in the art would determine the titer of the blocking antibody absent specific components of the kit claimed.

Claim 13-14 recite the limitation "blocking antibody" in line 2. There is insufficient antecedent basis for this limitation in the claim since only claim 12 mentions blocking antibodies. The remaining claims are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claim 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vold et al. (U.S. Pat. No.: 5,561,049) in view of Da Costa et al. (Biochim. Biophys. Acta, 1292, 23-30, 1996) and in further view of (Hoier-Madsen et al. –Int. J. Tiss Reac. XI (6), 327-332, 1989)

The claims are drawn to a method for detecting the presence of anti-folate receptor (FRs) auto antibodies in a biological sample of a subject. The method comprises the following steps:

- dissociating folate and the antibodies bound to a folate receptor (FR) by acidifying the sample containing them at a pH about 3.0 to pH about 5.0 in order to generate apo-FRs;
- removing the dissociated folate;
- incubating said biological sample with labeled folic acid (FA) at a pH about 8.0 to pH about 8.9 to obtain labeled-folate:FRs complexes;
- further incubating the above mentioned sample with labeled purified FRs (to compensate for a low concentration of endogenous FRs in the sample;

detecting and quantifying the formation of an immune complex between said anti-FRs auto antibodies present in said biological sample and said labeled purified FRs or previously labeled apo-FRs, wherein the presence of said immune complex indicates that said subject has anti-FRs auto antibodies.

The sample may be human serum.

Another independent claim is drawn to a method for detecting the presence of an autoantibody that blocks the binding of folate to FRs in a biological sample from a subject, comprising:

a. obtaining an FRs-bound matrix, wherein the matrix is placental membrane containing FRs from a human or homologous species.

b. dissociating folate bound to the FRs on said matrix and generating apo-FRs on said matrix by acidifying said matrix at a pH about 3.0 to pH about 5.0;

c. washing said matrix in the acid buffer to remove the dissociated folate;

d. resuspending said matrix in buffer, at a pH about 7.0 to pH about 8.6, and determining the folate binding capacity per unit volume by the binding of labeled folic acid;

e. removing free folate from said biological sample;

f. obtaining a control sample and removing free folate from said control sample;

g. incubating the suspended matrix from Step d with said biological sample from Step e in a buffer with a pH about 7.0 to pH about 8.6;

h. incubating the suspended matrix from Step d with said control sample from Step f, in a buffer with a pH of about 7.0 to 8.6;

i. washing said matrix from Step g and Step h;

j. incubating said matrix from Step i with labeled folic acid;

k. determining and quantifying the labeled folic acid binding capacity to said matrix from Step g and to said matrix from Step h, whereby a reduction of said labeled folic acid binding to said matrix in Step g compared to said labeled folic

acid binding to said matrix from Step h indicates the presence of auto antibodies that block the binding of folate to FRs in said subject.

The immune complex of the first claim is detected by formation of a second immune complex between said immune complex and an immunoglobulin- binding agent which can be a protein A membrane suspension or a detectably labeled second antibody. The immune complex might be detected by precipitating said immune complex using ammonium sulfate, sodium sulfate, alcohol, or polyethylene glycol. Also claimed is a test kit for detecting auto antibodies to FRs in a biological sample from a subject comprising purified FRs from a human or homologous species, reagents for treating said biological sample, labeled folic acid, and at least one indicator which detects a complex of said purified FRs and said auto antibodies. The indicator could be an enzyme, a radioactive label, fluorescent marker or biotin. Another test kit is claimed for detecting auto antibodies to FRs that block the binding of folate by the FRs in a biological sample from a subject comprising apo-FRs from a human or homologous species, reagents for treating said biological sample, labeled folio acid, and at least one indicator which detects said apo-FRs remaining in the reaction; also it contains reagents for detecting the titer of the blocking antibody or the apparent association constant to the blocking antibody.

Vold et al. teach methods of determining the presence or amount of antibodies in a sample suspected of containing the antibodies. On of the methods relates to the use of a first binding agent that binds the complex and does not bind the antigen when the antigen is not part of the complex, and to the use of a second binding agent that

selectively binds the antigen relative to binding the complex when the complex is bound to the first binding agent. The first binding agent can be bound to a soluble polymer or suspendable solid phase. The second binding agent can be bound to a solid phase. The second binding agent can also be two receptors that bind the antigen, where each receptor is bound to a signal producing system member. Also taught are kits to be used with the method (col. 3, lines 35-58; col.5, lines15-16). The sample may be an aqueous solution such as a body fluid from a host, for example, plasma or serum. The sample can be pretreated and can be prepared in any convenient medium which does not interfere with the assay (col. 4, lines 43-53). The signal producing system comprises one or more components, at least one component being a label, which generate a detectable signal that relates to the amount of bound and/or unbound label, i.e. the amount of label bound or not bound to the compound being detected. The label is any molecule that produces or can be induced to produce a signal, such as a fluorophor, an enzyme, chemiluminescent compound or photosensitizer a radioactive isotope or a dye. Thus, the signal is detected and/or measured by detecting enzyme activity, luminescence or light absorbance. The label is bound to a member of the specific binding participants which may be an antigen, or is capable of directly or indirectly binding the antigen, or is a receptor for the antigen, and includes, without limitation, the antigen; a ligand for a receptor bound to the antigen; a receptor for a ligand bound to the antigen; an antibody that binds the antigen; a receptor for an antibody that binds the antigen; a receptor for a molecule conjugated to an antibody to the antigen; an antigen surrogate capable of binding a receptor for the antigen; a ligand that binds the antigen

(col. 5, line 47 to col. 6, line 38). As an example, Vold et al. teach detecting auto antibodies to insulin; to glutamic acid decarboxylase ("GAD"); and to islet cell antigens. One method of determining the presence or amount of GAD human auto antibodies in a sample suspected of containing the auto antibodies, comprises the steps of bringing together in an aqueous medium: (i) the sample, (ii) GAD antigen that binds the auto antibodies to form an antigen: autoantibody complex, wherein the amount of antigen added to the medium is Z, wherein Z is within the range of X to nX and Z is less than Y, where n is 5-1000, preferably 10-100, X is the minimum amount of antigen that can be reliably detected when there are no antibodies present in a sample and Y is the maximum expected amount of antibodies in the sample, (iii) a first binding agent that, wherein the first binding agent is a receptor for the auto antibodies that binds the complex, and is bound to a material selected from the group consisting of a suspendable solid phase and a soluble polymer; adding to the medium a second binding agent that selectively binds the antigen relative to binding the complex when the complex is not separated from the medium; and detecting the binding of the second binding agent to the antigen, the binding thereof being related to the presence or amount of the auto antibodies in the sample. Recombinant GAD_{65} is labeled with biotin to provide bGAD. This conjugate is then incubated with patient serum samples. A suspension of Sepharose coupled to protein-A is then added and the incubation continued. The suspension is transferred to a microtiter well that has been coated with streptavidin. After incubation to bind free bGAD, the well is washed and incubated with a mouse monoclonal antibody to GAD, which is either conjugated to a label such as

horseradish peroxidase ("HRP") or unconjugated. When unconjugated antibodies are used, the well is washed again and then incubated with labeled anti-mouse IgG antibodies. In either case, after the labeled antibodies are added, the well is washed a final time and incubated with any additional binding members. For example, if the label is HRP, then the final incubation could include a solution containing hydrogen peroxide and tetramethylbenzidine, and color development would be read after incubation. (col. 13, lines 1-59). The reaction conditions taught by Vold et al. are subject to modification by those skilled in the art depending on the specific reagents and assay protocol chosen for any particular application. The methods can be applied to numerous types of assays such as heterogeneous or homogeneous, and the conditions and reagents used will be selected accordingly. The sample, preferably in a suitable medium, can be examined directly or may be pretreated before the sample is added to the assay medium. Pretreatment can render the antibody analyte more readily available to one or more of the assay reagents or more readily detectible by reducing interference in the assay by removing any unwanted materials. The sample may be pretreated to separate or lyse cells; precipitate, hydrolyze or denature proteins; hydrolyze lipids; or the like (col. 14, lines 37-55). The relative amounts of the various reagents used in the assay and packaged in the kits can be varied widely to provide for concentrations of the reagents that substantially optimize the reactions that need to occur during the present method and to further substantially optimize the sensitivity of any assay performed. For example, considerations such as the tradeoff between sensitivity and the assay range, the particular detection technique, and the concentration of the analyte will determine

the concentration of antigen used and will normally determine the concentration of the other reagents also. In addition, the final concentration of each of the reagents will normally be determined empirically to optimize the sensitivity of the assay over the range of interest. The method is preferably carried out preferably in an aqueous buffered medium at a moderate pH will be employed, generally that which provides optimum assay sensitivity; the pH for the medium will usually be in the range of about 5-10, preferably, in the range of about 7-9. The pH is chosen so as to maintain a significant level of binding between binding members, while optimizing signal producing proficiency (col. 14, line 60 to col. 15, line 34). Vold et al does not specifically address the detection of human auto antibodies against FRs and as such does not address the specific conditions (pH and binders).

Da Costa et al. purified and characterized a folate binding protein from placenta. They obtained the apo-folate receptor by lowering the pH of a solubilized membrane preparation to 3.5, thus dissociating the protein from the bound folate, which was adsorbed to charcoal (abstract). In the materials and methods section details are described for obtaining membrane bound FRs. The free endogenous folate was adsorbed by charcoal and pelleted. The ph of the supernatant solution containing the apo-FRs was raised to 7.4 and incubated with a folate affinity matrix. After affinity purification of apo-FR and elution of bound apo-FR with an acetic acid solution of pH 3, and folate binding capacity was determined using radiolabel folate (materials and methods section, p. 24). DaCosta et al. also teach that the immunogenic properties of both the membrane bound FR and soluble FRs are the same (p.28, left col.; table 2).

The authors also assayed the blocking properties of antibodies against FR by incubating the labeled folate with dilutions of the antiserum containing anti-FR antibodies (p. 25, subheading 2.4).

Hoier –Madsen et al. teach a method of detection of antibodies to folate binding-proteins from serum of patients of chronic inflammatory bowel disease (abstract and p. 328). Even though the method differs from the method of the instant Application, it provides evidence of the antibodies against the FR in the human serum.

At the time that the invention was made, the state of the art in the field of ligand binding assays, detection of antibodies and characterizing the titer of antibodies and association constants for protein: protein interactions is extremely well developed. Practically, all the variations of these reactions are considered routine, once the components to be involved in the interactions are disclosed. The choice of pH conditions for binding of dissociation or the choice of labels for the indicators is considered to be routine optimization. Once the characteristics of the molecules involved are known, because the nature of the binders dictates the conditions for the assays which are now standard. The examiner's position is supported by the decision in *KSR* 550 U.S. at ___, 82 USPQ2d at 1391 which recognizes that a person of ordinary skill in the art is always motivated to pursue the known options within her or his technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Applicants claim the auto antibodies to folate receptors to be the hallmark of their inventions. However, the existence of the antibodies was proved by Hoier-Madsen et al.

As iterated supra, due to the high skill existent in the art at the time that the invention was made the specific conditions of the general methods of Vold et al., such as the choice of pH conditions for binding of dissociation or the choice of labels for the indicators is considered to be routine optimization. Once the characteristics of the molecules involved are known, because the nature of the binders dictates the conditions for the assays which are now standard. Therefore it would have been obvious for a person of ordinary skill in the art to have optimized and adjust the conditions of Vold et al. to detect antibodies against FRs as taught by Hoier-Madsen et al. in the light of the characteristics of Folate receptors as taught by DaCosta et al with a good expectation of success. A person of ordinary skill in the art is always motivated to pursue the known options within her or his technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

14. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neurath AR (U.S. Pat. No. 4,459,539) in view of Da Costa et al. (Biochim. Biophys. Acta, 1292, 23-30, 1996) and in further view of (Hoier-Madsen et al. –Int. J. Tiss Reac. XI (6), 327-332, 1989).

Neurath teaches a process for determining the presence of an antigen or antibody in a sample wherein said antigen or antibody exists in the form of an immune complex which comprises:

A. contacting the immune complex originating from the sample suspected of containing immune complex with a dissociating buffer whereby said immune complex, if present, is dissociated into antigen and antibody;

B. contacting a solid support which binds proteins with said dissociating buffer suspected of containing antigen or antibody and removing said buffer;

C. washing said solid support;

D. adding protein to fill unoccupied sites on said solid support;

E. adding radioactively labeled or enzyme labeled antibody or antigen to said solid support, said labeled antibody or antigen corresponding to antigen or antibody on said solid support, incubating the resultant mass and washing the same;

F. measuring the radioactivity or enzymatic activity associated with the solid support (abstract). Neurath also provides examples for detection of immune complexes in human serum complexes. Neurath does not specifically address the detection of human auto antibodies against FRs and as such does not address the specific conditions (pH and binders).

The teachings of DaCosta et al and Hoier-Madsen et al. were presented supra.

As iterated supra, due to the high skill existent in the art at the time that the invention was made the specific conditions of the general method of Neurath, such as the choice of pH conditions for binding of dissociation or the choice of labels for the indicators is considered to be routine optimization. Once the characteristics of the molecules involved are known, because the nature of the binders dictates the conditions for the assays which are now standard. Therefore it would have been obvious for a

person of ordinary skill in the art to have optimized and adjust the conditions of Neurath to detect antibodies against FRs as taught by Hoier-Madsen et al. in the light of the characteristics of Folate receptors as taught by DaCosta et al with a good expectation of success. A person of ordinary skill in the art is always motivated to pursue the known options within her or his technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Holm et al. (Bioscience Reports, 16, 379-389, 1996) characterized a high-affinity folate receptor in human molar placenta tissue. Radioligand binding exhibited characteristics typical of other high-affinity folate binding proteins. Those included positive cooperativity, a tendency to increased binding affinity with decreasing receptor concentration, a slow ligand dissociation at pH 7.4 becoming rapid at pH 3.5, and inhibition by folate analogues. The folate receptor cross-reacted with antibodies against human milk folate binding protein, e.g. the syncytothrophoblastic layer of molar placenta tissue sections showed strongly positive immunostaining. The gel filtration profile contained two radioligand-bound peaks (25 and 100 kDa), however, with considerable overlap. Only a single band of 70kDa was seen on SDS-PAGE immunoblotting (abstract).

Holm et al. (Arch. Biochem and Biophys. 366, 183-191, 1999) teaches a folate receptor isoform homologous to human milk folate receptor protein seemed to prevail in serous ovarian carcinomas (abstract).

Lindstrom JM (U. S. Pat. No.: 4,789,640) teaches improved assays are provided for anti-acetylcholine receptor protein auto antibodies in the sera of patients with myasthenia gravis.

Michel et al. (U. S. Pat. No.: 5,741,654) provides an immunoassay for determining the presence and amount of LKM auto antibodies, which immunoassay comprises the steps of (a) contacting a test sample with LKM antigen and incubating the mixture for a time and under conditions sufficient to form LKM antigen/antibody complexes; (b) contacting the LKM antigen/antibody complexes with an indicator reagent which comprises an anti-human antibody or a fragment thereof attached to a signal generating compound, which signal generating compound is capable of generating a detectable measurable signal, and incubating this second formed mixture for a time and under conditions sufficient to form LKM antigen/antibody/indicator reagent complexes; and (c) detecting the measurable signal generated by the signal generating compound as an indication of the presence of LKM autoantibody in the test sample. Preferably, the capture antigen for LKM autoantibody is attached to a solid phase prior to its use in the assay. If a solid phase is used, it can be separated from the liquid phase prior to the detection of the signal generating compound. Moreover, steps (a) and (b) can be performed simultaneously. It also is contemplated and within the scope of the invention that the test sample can be diluted in all of the assay

embodiments, and that washing occurs or can occur between steps of all assay formats described herein.

Conclusion

16. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lorraine Spector/Ph.D.

Primary Examiner, Art Unit 1647